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(54) Medical device

(57) The invention relates to a medical device useful for the localized delivery of a therapeutic agent having at least one blood-contacting surface comprising a porous material having dispersed therein an elutable therapeutic agent. Preferred devices include a structure including a porous polymeric material and an elutable therapeutic agent in the form of a solid, gel, or neat liq-

uid, which is dispersed in at least a portion of the porous polymeric material. Methods for making a medical device having a blood-contacting surface are also provided. One method includes the use of a concentrating agent whereby to localise the therapeutic agent within the porous material. Another method involves multiple immersion steps without the use of a concentrating agent.

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Description

[0001] This invention relates to a medical device employing a therapeutic agent as a component thereof. In particular, the invention relates to a method for making a medical device capable of localized application of therapeutic agents.

[0002] Medical devices which serve as substitute blood vessels, synthetic and intraocular lenses, electrodes, catheters, and the like, in and on the body, or as extracorporeal devices intended to be connected to the body to assist in surgery or dialysis are well known. For example, intravascular procedures can bring medical devices into contact with the patient's vasculature. In treating a narrowing or constriction of a duct or canal, percutaneous transluminal coronary angioplasty (PTCA) is often used with the insertion and inflation of a balloon catheter into a stenotic vessel. Other intravascular invasive therapies include atherectomy (mechanical systems to remove plaque residing inside an artery), laser ablative therapy, and the like. However, the use of mechanical repairs can have adverse consequences for the patient. For example, restenosis at the site of a prior invasive coronary artery disease therapy can occur. Restenosis, defined angiographically, is the recurrence of a 50% or greater narrowing of a luminal diameter at the site of a prior coronary artery disease therapy, such as a balloon dilatation in the case of PTCA therapy. For example, an intra-luminal component of restenosis may develop near the end of the healing process initiated by vascular injury, which then contributes to the narrowing of the luminal diameter. This phenomenon is sometimes referred to as "intimal hyperplasia". It is believed that a variety of biologic factors are involved in restenosis, such as the extent of the injury, platelets, inflammatory cells, growth factors, cytokines, endothelial cells, smooth muscle cells, and extracellular matrix production, to name a few.

[0003] Attempts to inhibit or diminish restenosis often include additional interventions such as the use of intravascular stents and the intravascular administration of pharmacological therapeutic agents. Examples of stents which have been successfully applied over a PTCA balloon and radially expanded at the same time as the balloon expansion of an affected artery include the stents disclosed in US-A-4,733,665 (Palmaz), US-A-4,800,882 (Gianturco), and US-A-4,886,062 (Wiktor).

[0004] Also, such stents employing therapeutic agents such as glucocorticoids (e.g. dexamethasone, beclamethasone), heparin, hirudin, tocopherol, angiopoetin, aspirin, ACE inhibitors, growth factors, oligonucleotides and, more generally, antiplatelet agents, anti-coagulant agents, antimitotic agents, antioxidants, antimetabolite agents, and anti-inflammatory agents have been considered for their potential to solve the problem of restenosis. Such substances have been incorporated into (or onto) stents by a variety of mechanisms. These mechanisms involve incorporating the therapeutic

agents into polymeric coatings and films, including hydrogels, as well as covalently binding the therapeutic agents to the surface of the stent.

[0005] For example, therapeutic agents have been dissolved or dispersed in a solution of polymer in an organic solvent. This is then sprayed onto the stent and allowed to dry. Alternatively, therapeutic agents have been incorporated into a solid composite with a polymer in an adherent layer on a stent body with fibrin in a separate adherent layer on the composite to form a two layer system. The fibrin is optionally incorporated into a porous polymer layer in this two layer system. The therapeutic agent, however, is incorporated into the underlying solid polymer. The overlying porous polymer layer provides a porous barrier through which the therapeutic agent is transferred.

[0006] Conventional methods of loading the therapeutic agent into a polymer, such as spray coating, do not provide high concentrations of therapeutic agents. Typically, upon spray coating a therapeutic agent onto a stent body, only about 2% of the spray is captured by the stent. This can be prohibitively expensive for therapeutic agents that are extremely costly and scarce, such as peptidic drugs.

[0007] Thus, a need exists for a medical device, preferably a stent, having a therapeutic agent incorporated therein at sufficiently high concentrations that the therapeutic agent can be delivered over an extended period of time. Improved methods by which the therapeutic agent can be incorporated into the porous polymeric material with lower levels of waste are also needed.

[0008] It has now been found that medical devices have improved properties in this regard where they comprise a porous material, preferably a porous polymeric material, with a therapeutic agent incorporated therein. Typically, such devices will comprise a porous polymeric layer in the form of a coating or film.

[0009] Viewed from one aspect the invention thus provides a medical device having at least one blood-contacting surface comprising a porous material having dispersed therein an elutable therapeutic agent. Substrates having at least one blood-contacting surface comprising a porous material having dispersed therein an elutable therapeutic agent form a further aspect of the invention.

[0010] Preferably, the device according to the invention is capable of applying a highly localized therapeutic agent into a body lumen to treat or prevent injury. For example, in an arterial site treated with percutaneous transluminal coronary angioplasty therapy for obstructive coronary artery disease a therapeutic antithrombotic substance such as heparin may be included within a device and delivered locally in the coronary artery.

[0011] As used herein, the term "injury" means a trauma, that may be incidental to surgery or other treatment methods, e.g. deployment of a stent, or a biologic disease, such as an immune response or cell proliferation caused by the administration of growth factors. In addi-

tion, the device of the invention may be used in anticipation of "injury" as a prophylactic. A prophylactic treatment is one that is provided in advance of any symptom of injury in order to prevent injury, prevent progression of injury or attenuate any subsequent onset of a symptom of such injury.

[0012] In accordance with the invention, a device for delivery of localized therapeutic agent preferably includes a structure including a porous material and an elutable (i.e. capable of being dissolved under physiological conditions) therapeutic agent in the form of a solid, gel, or neat liquid, which is dispersed throughout at least a portion, and preferably a substantial portion, of the porous material. Preferably, the device is capable of being implanted in a body so that the localized therapeutic agent can be delivered in vivo, typically at a site of vascular injury or trauma. Preferably, the porous material is biocompatible, sufficiently tear-resistant, and non-thrombogenic.

[0013] The porous material may be a layer (e.g. a film, i.e. a sheet material or a coating) on at least a portion of the structure. Alternatively, the porous material may comprise an integral portion of the structure. Preferably, the porous material is a polymeric material selected from the group of a natural hydrogel, a synthetic hydrogel, silicone, polyurethane, polysulfone, cellulose, polyethylene, polypropylene, polyamide, polyester, polytetrafluoroethylene, and a combination of two or more of these materials. Examples of natural hydrogels include fibrin, collagen, elastin, and the like. More preferably, the porous polymeric material is a non-swelling biostable polymer selected from the group of silicone, polyurethane, polysulfone, cellulose, polyethylene, polypropylene, polyamide, polyester, polytetrafluoroethylene, and a combination of two or more of these materials.

[0014] Viewed from a further aspect the invention thus provides a medical device having at least one blood-contacting surface comprising:

a porous polymeric material comprising a non-swelling biostable polymer; and
an elutable therapeutic agent in the form of a solid, gel, or neat liquid, which is dispersed in at least a portion of the porous polymeric material.

[0015] The therapeutic agent can be one or more of a wide variety of therapeutic agents, including peptidic drugs. Preferably, the therapeutic agent includes an antithrombotic material. More preferably, the antithrombotic material is a heparin or heparin derivative or analog. Such therapeutic agents are soluble in water such that they elute from the porous polymeric material.

[0016] The structure of the device can be adapted for its intended extracorporeal or intravascular purpose in an internal human body site, such as an artery, vein, urethra, other body lumens, cavities, and the like or in an extracorporeal blood pump, blood filter, blood oxygena-

tor or tubing. In one aspect of the invention, the shape is preferably generally cylindrical, and more preferably, the shape is that of a catheter, a stent, or a guide wire. In particularly preferred embodiments, the medical device is an intraluminal stent, preferably having a porous polymeric film thereon.

[0017] In a yet further aspect the invention thus provides an intraluminal stent comprising:

10 a generally cylindrical stent body; and
an adherent layer on the stent body comprising a porous polymeric material and an elutable therapeutic agent in the form of a solid, gel, or neat liquid, which is dispersed in at least a portion of the porous polymeric material.

[0018] The invention also provides methods for making a medical device which includes therapeutic agents. In one embodiment, a method of the invention includes: 20 providing a structure comprising a porous material; contacting the structure comprising a porous material with a concentrating agent to disperse the concentrating agent throughout at least a portion of the porous material; contacting the structure comprising a porous material and the concentrating agent with a solution of a therapeutic agent; and removing the therapeutic agent from solution within the porous material at the locations of the concentrating agent.

[0019] The present invention also provides a method 30 for making a medical device that includes: providing a structure comprising a porous material; immersing the structure comprising a porous material in a saturated solution of a therapeutic agent for a sufficient period of time to allow the solution to fill the porous material; removing the medical device from the solution; drying the medical device; and repeating the steps of immersing, removing, and drying to provide a therapeutic agent dispersed within the porous material. Preferably, the method further includes the step of removing air bubbles from the

40 porous material while being immersed in the solution of the therapeutic agent. The step of removing air bubbles from the porous material can include applying ultrasonics, reduced pressure, elevated pressure, or a combination thereof, to the solution. Preferably, the method involves loading a stent having a porous polymeric film thereon, and subsequently applying an overlayer of a polymer.

[0020] A therapeutic agent may be loaded onto a structure including a porous material at any number of 50 points between, and including, the point of manufacture and the point of use. For example, the device can be stored and transported prior to incorporation of the therapeutic agent. Thus, the end user can select the therapeutic agent to be used from a wider range of therapeutic agents.

[0021] Medical devices obtained by the methods of the invention form a further aspect of the invention.

[0022] One of the more preferred configurations for a

device according to the invention is a stent for use in artery/vascular therapies. The term "stent" refers to any device capable of being delivered by a catheter and which, when placed into contact with a portion of a wall of a lumen to be treated, will also deliver localized therapeutic agent at a luminal or blood-contacting portion of the device. A stent typically includes a lumen wall-contacting surface and a lumen-exposed surface. Where the stent is shaped generally cylindrical or tube-like, including a discontinuous tube or ring-like structure, the lumen-wall contacting surface is the surface in close proximity to the lumen wall whereas the lumen-exposed surface is the inner surface of the cylindrical stent. The stent can include polymeric or metallic elements, or combinations thereof, onto which a porous material is applied. For example, a deformable metal wire stent is useful as a stent framework of this invention, such as that described in US-A-4,886,062 (Wiktor), which discloses preferred methods for making a wire stent. Other metallic stents useful in this invention include those of US-A-4,733,655 (Palmaz) and US-A-4,800,882 (Gianturco).

[0023] Other medical devices, such as heart valves, vascular grafts, pacing leads, etc., can also include the embodiments of the present invention. As used herein, medical device refers to a device that has surfaces that contact tissue, blood, or other bodily fluids in the course of their operation, which fluids are subsequently used in patients. This can include, for example, extracorporeal devices for use in surgery such as blood oxygenators, blood pumps, blood sensors, tubing used to carry blood and the like which contact blood which is then returned to the patient. This can also include endoprostheses implanted in blood contact in a human or animal body such as vascular grafts, stents, pacemaker leads, heart valves, and the like that are implanted in blood vessels or in the heart. This can also include devices for temporary intravascular use such as catheters, guide wires, and the like which are placed into the blood vessels or the heart for purposes of monitoring or repair.

[0024] Referring now to Figure 1, the stent 20 comprises a stent framework 22 and a porous material coating 24. The stent framework 22 is deformable and can be formed from a polymeric material, a metal, or a combination thereof. A balloon 15 is positioned in Figure 1 adjacent the lumen-exposed surface of the stent to facilitate delivery of the stent. The stent 20 can be modified to increase or to decrease the number of wires provided per centimeter in the stent framework 22. Similarly, the number of wire turns per centimeter can also be modified to produce a stiffer or a more flexible stent framework.

[0025] Polymeric stents can also be used in this invention. The polymers can be non-bioabsorbable or partially or totally bioabsorbable. Stents of this invention can be completely non-bioabsorbable, totally bioabsorbable or a composite of bioabsorbable polymer and non-absorbable metal or polymer. For example, another

stent suitable for this invention includes the self-expanding stent of resilient polymeric material as disclosed in WO 91/12779 (Medtronic, Inc.).

[0026] 5 Non-bioabsorbable polymers can be used as alternatives to metallic stents. The stents of this invention should not substantially induce inflammatory and neointimal responses. Examples of biostable non-absorbable polymers that have been used for stent construction with or without metallic elements include polyethylene terephthalate (PET), polyurethane urea, and silicone. Although the porous material is shown as a coating 24, it is to be understood that, for the purposes of this invention, the porous material can be incorporated into the material of the stent.

[0027] 10 Referring to Figure 2, an alternative stent 30 is shown. The stent framework 34 is affixed with a film of a porous material 32. This can be accomplished by wrapping the film 32 around the stent framework 34 and securing the film 32 to the framework 34 (i.e. the film is usually sufficiently tacky to adhere itself to the framework but a medical grade adhesive could also be used if needed) so that the film 32 will stay on the balloon 36 and framework 34 until it is delivered to the site of treatment. The film 32 is preferably wrapped over the framework with folds or wrinkles that will allow the stent 30 to be radially expanded into contact with the wall of the lumen to be treated. Alternatively, the film 32 can be molded to the stent framework 34 such that the framework 34 is embedded within the film 32. Preferably, the film 32 is located on a lumen-wall contacting surface 33 of the stent framework 34 such that therapeutic material is substantially locally delivered to a lumen wall, for example, an arterial wall membrane (not shown).

[0028] 15 As mentioned above, the device according to the invention is generally a structure including a porous material. In one embodiment, the porous material includes a polymeric film or coating on at least a portion of the structure. In another embodiment, the porous material is an integral portion of the structure. Preferably, the porous material is a biocompatible polymer and is sufficiently tear-resistant and non-thrombogenic. Examples of suitable polymers include those disclosed in US-A-5,679,400 (Tuch). More preferably, the porous material is selected from the group of a natural hydrogel, a synthetic hydrogel, silicone, polyurethane, polysulfone, cellulose, polyethylene, polypropylene, polyamide, polyester, polytetrafluoroethylene, and a combination of two or more of these materials. Examples of natural hydrogels include fibrin, collagen, elastin, and the like. In materials which do not include pores in their usual structural configurations, pores of about 10 μm in diameter or as large as 1000 μm in diameter can be introduced by conventional means such as by introducing a solvent and dissolving the particulate material with a solvent. [0029] 20 Typically, and preferably, the porous material is in the form of a sheet material or coating of a non-swelling biostable polymer. As used herein, a "non-

swelling biostable" or "non-swellable biostable" polymer is one that does not absorb a significant amount of water (i.e. it absorbs less than about 10% by weight water) and it is not readily degraded in the body. Such non-swelling biostable polymers include, for example, silicone, polyurethane, polysulfone, cellulose, polyethylene, polypropylene, polyamide, polyester, polytetrafluoroethylene, and combinations thereof. If the polymer is biodegradable, the rate at which it degrades is slower than the rate at which the therapeutic agent elutes.

[0030] If the porous material is in the form of a porous sheet (i.e. film) or coating, it can be made by a variety of methods. These methods can include, for example, using a solid particulate material (also referred to herein as pore-forming material) that can be substantially removed after the film or coating is formed, thereby forming pores. By using a solid particulate material during film or coating formation, the size of the pores can, to some extent, be controlled by the size of the solid particulate material being used. The particulate material can range from less than about 1 μm in diameter to about 1000 μm , preferably from about 1 μm to about 100 μm , more preferably about 5 μm to about 50 μm . For uniformity of pores, the particulate material can be screened through successively finer mesh sieves, e.g. through 100, 170, 270, 325, 400, and 500 mesh analytical grade stainless steel mesh sieves, to produce a desired range of particle sizes.

[0031] The particulate material may include inorganic and organic particulate material, including, for example, sodium chloride, lithium chloride, sucrose, glucose, sorbitol, sodium citrate, sodium ascorbate, urea, citric acid, dextran, poly(ethylene glycol), sodium nitroprusside, mannitol, sodium bicarbonate, ascorbic acid, sodium salicylate, or combinations thereof. It will be understood by one of skill in the art that a mixture of different particulate materials can be used if desired. Also, it will be understood by one of skill in the art that because a portion of the particulate material may remain within the film, it is preferred that the solid particulate material be biocompatible.

[0032] Typically, the particulate material chosen is less soluble than the polymer in the chosen solvent (e.g. water or an organic solvent) used to deposit or form the polymer. The particulate material may actually be soluble in the solvent; however, to form pores, it only has to be less soluble than the polymer in the solvent of choice. As the solvent is removed from the solution, the pore-forming material will precipitate out of solution and form particles surrounded by the polymer, which is still in solution. The polymer will then come out of solution as more solvent is removed and the particles will be dispersed within the polymer. After the solvent is removed, the particulate material is removed using a liquid in which the polymer is not soluble, thereby forming pores.

[0033] In one method according to the present invention, a porous sheet material (e.g. polyurethane sheet

material) can be made by dissolving a polymer (e.g. polyether urethane) in an organic solvent (e.g. 1-methyl-2-pyrrolidone); mixing into the resulting polymer solution a crystalline, particulate material (e.g. sodium chloride, sucrose, etc.) that is not soluble in the solvent; casting the solution with particulate material into a thin film; and then applying a second solvent (e.g. water), to dissolve and remove the particulate material, thereby leaving a porous sheet. Such a method is disclosed in US-A-

5,591,227 (Dinh et al.) and US-A-5,599,352 (Dinh et al.).

[0034] Preferably, a combination of soluble and insoluble particulate material may be used to create a broader range of pore sizes. The use of a soluble particulate material, such as poly(ethylene glycol), may create small (< 2 μm diameter) interconnecting pores that create a solvent path for the removal of the larger (e.g. 50 μm diameter) particles, which may not be in particle-to-particle contact.

[0035] A suspension of particulate material may be created by first dissolving the particulate in a solvent, then precipitating the mixture in a solution of polymer in a second solvent in which the particulate is insoluble. For example, an 8% solution of sodium nitroprusside in ethanol can be added with rapid stirring to a 2% solution

25 of polyurethane in tetrahydrofuran. The sodium nitroprusside precipitates to form a suspension of less than about 5 μm particles.

[0036] The weight ratio of pore-forming material to polymer in a coating composition may range from about 30 1:3 to about 9:1, preferably about 2:1 to about 9:1, although this is not necessarily limiting. In theory, the porosity is limited by the toughness of the polymer.

[0037] A smooth coating may be obtained by applying an atomized spray to the stent. The spray should be applied at a rate such that evaporation prevents the accumulation of sufficient liquid to form drips along the stent. A macroscopically smooth surface may also be obtained by keeping the particle size less than about $\frac{1}{4}$ of the coating or film thickness.

[0038] Although films (i.e. sheet materials) for medical devices, particularly stent bodies, according to the present invention can be manufactured separately from the support structure of the medical device and attached to the support structure after formation, preferred methods include forming the films directly on the support structure such that the support structure is at least partially, preferably completely, encapsulated by the film (i.e. sheet material).

[0039] Alternatively, medical devices can include a 50 coating of a porous polymer made by spraying a solution of the polymer and particulate material directly on the support. In this way, the coating does not necessarily form a film that encapsulates the device; rather it forms a coating around the structure (e.g. wire) of the device.

[0040] The geometry of the porous material (coated wires vs. sheets or films) depends on the coating substrate and is largely independent of the pore forming and application methods used. A film can be made by spraying, dip-

ping, or sheet, casting, as long as the mandrel is a rod or a flat sheet. The stent wires can be coated by any of these methods as well, although most preferably, they are coated by spraying to prevent droplet formation.

[0040] In one such method, which is disclosed in WO 97/07973 (Medtronic, Inc.), a stent is placed on a mandrel. A particulate material is then applied to the mandrel and stent such that it is lightly adhered to the mandrel. The particulate material should be readily soluble in a solvent which will not also dissolve the polymer chosen for the film. For example, crystalline sodium bicarbonate is a water soluble material that can be used as the particulate material. A non-aqueous liquid, preferably a solvent for the polymer film material, can be applied to the mandrel before applying the particulate material in order to retain more of the particulate material on the mandrel. For example, when a polyurethane is to be used for the film material, the solvent 1-methyl-2-pyrrolidinone (NMP) can be used to wet the surface of the mandrel before the application of particulate material. Preferably, the mandrel is completely dusted with the particulate in the portions of the mandrel to be coated with the polymer film. This can be accomplished by dipping the mandrel in NMP, allowing it to drain vertically for a few seconds and then dusting the sodium bicarbonate onto the mandrel while rotating it horizontally until no further bicarbonate particles adhere. Excess particulate material can be removed by gently tapping the mandrel.

[0041] Coating with polymer may proceed immediately following application of the particulate material. A polymer is provided in a dilute solution and is applied to the particle-coated stent and mandrel. For example, polyurethane can be dissolved in NMP to make a 10% solution. Gel particles and particulate impurities can be removed from the solution by use of a clinical centrifuge. The polymer solution can be applied by dipping the mandrel into the solution and letting the solvent evaporate. With the solution of polyurethane and NMP, a single dip in the solution can provide a film of adequate thickness. To assist in the formation of communicating passageways through the polymer between the blood-contacting surface and the lumen-contacting surface, additional sodium bicarbonate particles are preferably dusted onto the polymer solution immediately after the dipping operation and before the polymer solution has dried. Excess particulate material can be removed by gently tapping the mandrel. To precipitate and consolidate the polyurethane film on the stent, it can be dipped briefly (about 5 minutes) in water and then rolled gently against a wetted surface, such as a wet paper towel. The stent assembly can then be placed into one or more water baths over an extended period (e.g. 8 hours) to dissolve and remove the sodium bicarbonate. After drying in air at temperatures from about 20°C to about 50°C, the film can then be trimmed to match the contour of the wire.

[0042] In yet another method, a solvent in which the polymer is soluble that is capable of phase separating from the polymer at a reduced temperature can be used

to prepare a porous polymer film. In this method, the stent or other medical device is placed in a cavity of a mold designed for forming a film around the stent, similar to that disclosed in US-A-5,510,077 (Dinh et al.). A

5 solution of the desired polymer, such as polyurethane, dissolved in a solvent, such as dioxane, is added to the mold. The temperature of the solution is then reduced to a temperature at which the solvent freezes and phase separates from the polymer, thereby forming particulate material (i.e. frozen solvent particles) *in situ*. Typically, for polyurethane in dioxane, this is a temperature of about -70°C to about 3°C. The composition is then immersed in an ice cold water bath (at about 3°C) for a few days to allow the dioxane to dissolve into the ice cold water, thereby forming pores. The number and size of the pores can be controlled by the concentration of the polymer and the freezing temperature. A method similar to this is disclosed in Liu et al., J. Biomed. Mater. Res. 26: 1489, 1992. This method can be improved on by using a two-step freezing process as disclosed in U. S. Pat. Application. Ser. No. 09/069,659, filed on April 29, 1998.

[0043] In yet another embodiment, a porous material can be created from a mixture of a low boiling good solvent and a higher boiling poor solvent, in which the polymer is soluble. After application to the target substrate, the lower boiling good solvent evaporates preferentially until a point is reached where the polymer precipitates from the remaining solvent mixture, which is relatively richer in the poor solvent. The polymer precipitates in and around pockets of the poor solvent, creating a porous structure. The number and size of pores can be controlled by the boiling points of the two solvents, the concentration of polymer and the drying rate. An example is a 1% solution of poly(1-lactic acid) (PLLA) in a 60: 30 mixture of chloroform:iso-octane. As the chloroform evaporates, the PLLA precipitates from the iso-octane to create an opaque PLLA coating containing 2-5 µm pores. This method is further described in US-A-5,679,400 (Tuch).

[0044] The therapeutic agent used in the present invention may be any therapeutic agent which possesses desirable therapeutic characteristics and which can be provided in a form that can be solubilized, for example, 45 by water or an organic solvent, and are capable of being eluted from the porous polymeric material in the body of a patient. Preferred therapeutic agents are solids, gels, or neat liquids (i.e. materials not dissolved in a solvent) at ambient temperature (i.e. about 20-25°C), and preferably at body temperatures, that are capable of being eluted from the porous polymeric material in the body of a patient. For example, antithrombotics, antiplatelet agents, antimitotic agents, antioxidants, antimetabolite agents, anti-inflammatory agents, enzyme inhibitors, and anti-angiogenic factors as disclosed in US-A-5,716,981 (Hunter et al.) could be used. Anticoagulant agents, such as heparin, heparin derivatives, and heparin analogs, could also be used to prevent the for-

mation of blood clots on the device.

[0045] A structure having a porous material, preferably a porous polymeric material, can be loaded with one or more therapeutic agents using a wide variety of methods. For example, the porous material can be immersed in a solution or dispersion of the therapeutic agent in a solvent. The solution (preferably, a supersaturated solution) or dispersion is allowed to fill the pores and the solvent is allowed to evaporate leaving the therapeutic agent dispersed within at least a portion of the pores. The solvent can be water or an organic solvent that does not dissolve the polymer. If the solvent does not dissolve the therapeutic agent, the particles of the therapeutic agent are smaller than the pore openings. Alternatively, in certain embodiments, the solvent can be chosen such that it swells the polymer, thereby achieving a greater level of incorporation of the therapeutic agent.

[0046] The following methods for loading one or more therapeutic agents into porous material are improved over prior art methods, such as spray coating methods. Although the same amount of therapeutic agent can be loaded onto a medical device, significantly less (e.g. about 100x less) waste of the therapeutic agent occurs using the following methods. This is particularly important for expensive therapeutic agents, such as peptidic drugs.

[0047] In one embodiment of the invention, filling of the pores can be enhanced through the use of ultrasonics, vacuum, and/or pressure. While the device is submerged in solution, ultrasonic energy or vacuum can be used to accelerate the removal of air bubbles from the pores allowing the pores to fill with the solution containing the therapeutic agent. Hyperbaric pressure on the solution may cause the air in the pores to be dissolved in the solution, thereby allowing the pores to fill with liquid. Furthermore, the level of incorporation can be increased by using multiple dip-vacuum-dry cycles. If the therapeutic agent saturates the solution by 10% by volume, for example, when the solvent evaporates the pores will be 10% filled with the agent. Repeating the cycle will fill the remaining 90% void space and fill an additional 9% of the original pore volume. Further cycles continue the trend. For this procedure to be effective, however, the solution is saturated so that the previously deposited agent does not dissolve in subsequent cycles.

[0048] Preferably, a method of the invention includes loading a structure comprising a porous material with a concentrating agent, which may be a precipitating agent (e.g. a binding agent, sequestering agent, nucleating agent, etc.), a seed crystal, or the like, dispersed throughout at least a portion, preferably, a substantial portion, of the porous material, and subsequently loading the structure comprising a porous material and the concentrating agent with a solution of a therapeutic agent, wherein the therapeutic agent is removed from solution (e.g. as by crystallization and/or precipitation) within the porous material at the locations of the con-

centrating agent. This is a significantly improved method in that the concentrating agent provides a driving force for localization of the drug within the pores of the polymer. That is, it is believed that the concentrating agent provides a thermodynamically favourable surface for crystallization or precipitation.

[0049] The concentrating agent can be a precipitating agent or a seed crystal, for example, or any substance that can cause the therapeutic agent to fall out of solution.

10 [0049] As used herein, a seed crystal is a solid material that is the same as the therapeutic agent being deposited. As used herein, a precipitating agent is a solid material that is different from the therapeutic agent being deposited. It can include, for example, materials that

15 have a particular affinity for the therapeutic agent of interest, such as binding agents, sequestering agents, nucleating agents, and mixtures thereof. Examples of sequestering agents include heparin to sequester heparin, binding growth factors such as bFGF and, for example,

20 cyclodextrins to trap appropriately sized therapeutic agents to fit in their ring structures. Examples of binding agents include polycations (e.g. protamine) and poly-anions (e.g. heparin sulfate) for binding anionic and cationic therapeutic agents, respectively. The binding agent can also include a counterion of a salt that is insoluble upon complexation with the therapeutic agent in the solvent used in the solution of the therapeutic agent.

[0050] The solution containing the therapeutic agent is preferably a supersaturated solution, although this is not a necessary requirement. This can be prepared at elevated temperatures taking into consideration the limits of stability of the therapeutic agents and the porous material. The porous polymeric material with concentrating agent therein can be immersed in a solution of

30 the therapeutic agent in a solvent. The solution is allowed to fill the pores and the therapeutic agent allowed to come out of solution (e.g. as by the formation of crystals). The solvent can be water or an organic solvent that does not dissolve the porous polymer, although it

35 may swell the polymer as described above. The choice of solvent is one that is compatible with the therapeutic agent and porous material of choice. Filling of the pores can be enhanced through the use of ultrasonics, vacuum, and/or pressure, as well as by using multiple dip-vacuum-dry cycles, as described above.

[0051] Crystal and/or precipitate formation can be initiated by a variety of mechanisms. They may spontaneously form, by a variety of mechanisms. They may spontaneously form. Alternatively, the solution of the

50 therapeutic agent within the pores may need to be cooled to initiate crystallization and/or precipitation. It may be possible to initiate crystallization and/or precipitation by changing the pH and/or ionic strength of the solution of the therapeutic agent within the pores.

55 [0052] The initial concentrating agent, which may be a solid, liquid, or a gel, can be placed in the pores of the porous material by a variety of methods. For example, if the concentrating agent is a seed crystal of the thera-

peutic agent of interest, immersing the porous material in a solution or dispersion of the therapeutic agent in a solvent, allowing it to fill the pores, and allowing the solvent to evaporate, provides the therapeutic agent dispersed within at least a portion of the pores, as described above. Similarly, if the concentrating agent is a precipitating agent, the porous material can be immersed in a solution of this agent.

[0053] The methods of the present invention are advantageous in that the structure can be loaded with the therapeutic agent *in situ*, i.e. at or near the point of therapeutic use, typically before administration, preferably implantation, to a patient. This is particularly useful because the device can be stored and transported prior to incorporation of the therapeutic agent. This feature has several advantages. For example, the relevant consumer can select the therapeutic agent to be used from a wider range of therapeutic agents. Thus, the therapeutic agent selected is not limited to only those supplied with the device but can instead be applied according to the therapy required.

[0054] In order to provide additional control over the elution of the therapeutic agent, an overlayer may be applied to the medical device, as is disclosed in US-A-5,679,400 (Tuch), US-A-5,624,411 (Tuch), and US-A-5,624,411 (Tuch). The overlayer, typically in the form of a porous polymer, is in intimate contact with the therapeutic agent and allows it to be retained on the medical device. It also controls the administration of the therapeutic agent following implantation. For a stent, an overlayer is particularly desirable to retain the therapeutic agent on the stent during expansion of the stent.

[0055] The invention will now be described further by way of illustration with reference to the following non-limiting example and to the accompanying drawings, in which:

Figure 1 is an elevational view of one embodiment of a device according to the invention with a balloon catheter as a mode of delivery of the device; and Figure 2 is an elevational view of another embodiment of a device according to the invention with a balloon catheter as a mode of delivery of the device.

[0056] In the Example which follows, all parts, percentages, ratios, etc. are by weight unless otherwise indicated.

Example

[0057] Wiktor stents were coated as follows: 4 g of a 5 wt% solution of polyurethane as disclosed in US-A-4,873,308 (Coury et al.) in tetrahydrofuran (THF) and 20 g of a 5 wt% solution of citric acid in THF were combined and sprayed onto Wiktor stents using an air brush, similar to the method disclosed in US-A-5,679,400 (Tuch). Citric acid was extracted with deionized water for 10 minutes. The stent was then air dried at ambient

temperature and weighed. The porous polyurethane coating weights were 0.5-0.7 mg.

[0058] Into a microcentrifuge tube was added 0.12 g tissue factor pathway inhibitor (TFPI) and 1.0 ml sterile water. This was agitated to dissolve the TFPI. The polyurethane coated stents were immersed in the TFPI solution, which was subjected to reduced pressure (28 inches (94.8 kPa) of Hg) to evacuate the air from the pores. The stents were air dried and the immersion/vacuum process was repeated twice. After the last immersion process, stents were air dried at ambient temperature for 20 minutes. Each stent was immersed for less than two seconds in deionized water to remove TFPI on the surface of the stents. The stents were then dried in ambient temperature under vacuum for about 12 hours. The stents were weighed to determine the amount of TFPI loaded into the pores, which ranged from 0.15 mg to 0.33 mg.

[0059] Half the stents were overcoated with a 2 wt% solution of polyurethane solution in THF using the spray coating method described above, resulting in a coating weight of 0.6 mg. These stents were tested for elution. The stents with the overcoating eluted more slowly than the stents without the overcoating.

Claims

1. A medical device having at least one blood-contacting surface comprising a porous material having dispersed therein an elutable therapeutic agent.
2. A medical device as claimed in claim 1 having at least one blood-contacting surface comprising:
 3. a porous polymeric material; and an elutable therapeutic agent in the form of a solid, gel, or neat liquid, which is dispersed in at least a portion of said porous polymeric material.
 4. A medical device as claimed in claim 1 or claim 2 wherein said porous material comprises a film.
 5. A medical device as claimed in claim 1 or claim 2 wherein said porous material comprises an integral portion of the device.
 6. A medical device as claimed in any one of claims 1 to 4 wherein said porous material is a natural hydrogel, a synthetic hydrogel, silicone, polyurethane, polysulfone, cellulose, polyethylene, polypropylene, polyamide, polyester, polytetrafluoroethylene, or a combination of two or more of these materials.
 7. A medical device as claimed in any one of claims 1 to 5 wherein said porous material comprises a non-swelling biostable polymer.

7. A medical device as claimed in any preceding claim wherein said therapeutic agent comprises an anti-thrombotic material.

8. A medical device as claimed in claim 7 wherein the antithrombotic material is heparin, a heparin derivative or analog. 5

9. A medical device as claimed in any of one of claims 1 to 6 wherein said therapeutic agent is a peptidic drug. 10

10. A medical device as claimed in any preceding claim having a generally cylindrical or sheet-like shape. 15

11. A medical device as claimed in any preceding claim comprising a catheter, a stent, or a guide wire.

12. A medical device as claimed in claim 11 comprising an intraluminal stent. 20

13. An intraluminal stent comprising:

a generally cylindrical stent body; and an adherent layer on the stent body comprising a porous polymeric material and an elutable therapeutic agent in the form of a solid, gel, or neat liquid, which is dispersed in at least a portion of the porous polymeric material. 25

14. A method for making a medical device, said method comprising the steps of:

(a) providing a structure comprising a porous material;

(b) contacting said structure with a concentrating agent whereby to disperse the concentrating agent throughout at least a portion of the porous material;

(c) contacting said structure comprising a porous material and the concentrating agent with a solution of a therapeutic agent; and

(d) removing the therapeutic agent from solution within the porous material at the locations of the concentrating agent. 30

15. A method as claimed in claim 14 wherein said concentrating agent is selected from the group of a binding agent, a sequestering agent, a nucleating agent, a seed crystal, or a combination thereof. 35

16. A method as claimed in claim 14 or claim 15 wherein step (d) is effected by reducing the temperature, changing the pH or changing the ionic strength of the solution of the therapeutic agent. 40

17. A method for making a medical device, said method comprising the steps of:

(a) providing a structure comprising a porous material;

(b) immersing said structure in a saturated solution of a therapeutic agent for a sufficient period of time to allow the solution to fill the porous material;

(c) removing the structure from the solution;

(d) drying the structure; and

(e) repeating steps (b) through (d) whereby to provide a therapeutic agent dispersed within the porous material. 45

18. A method as claimed in claim 17 further comprising a step of removing air bubbles from the porous material while immersed in the solution of the therapeutic agent. 50

19. A method as claimed in claim 18 wherein the step of removing air bubbles from the porous material is effected by applying ultrasonics, reduced pressure, elevated pressure, or a combination thereof, to the solution. 55

20. A method as claimed in any one of claims 14 to 19 further comprising the step of applying an overlayer of a polymer to said structure.

21. A method as claimed in any one of claims 14 to 20 wherein said porous material is a natural hydrogel, a synthetic hydrogel, silicone, polyurethane, polysulfone, cellulose, polyethylene, polypropylene, polyamide, polyester, polytetrafluoroethylene, or a combination of two or more of these materials. 60

22. A method as claimed in any one of claims 14 to 21 wherein said therapeutic agent is an antithrombotic material. 65

23. A medical device obtainable by a process as claimed in any one of claims 14 to 22. 70

24. A substrate having at least one blood-contacting surface as defined in any one of claims 1 to 9. 75



(19)

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(54) Medical device

(57) The invention relates to a medical device useful for the localized delivery of a therapeutic agent having at least one blood-contacting surface comprising a porous material having dispersed therein an elutable therapeutic agent. Preferred devices include a structure including a porous polymeric material and an elutable therapeutic agent in the form of a solid, gel, or neat li-

uid, which is dispersed in at least a portion of the porous polymeric material. Methods for making a medical device having a blood-contacting surface are also provided. One method includes the use of a concentrating agent whereby to localise the therapeutic agent within the porous material. Another method involves multiple immersion steps without the use of a concentrating agent.

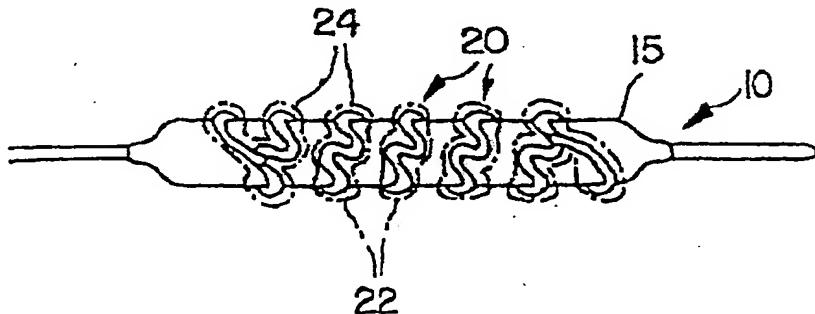


FIG. 1

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EUROPEAN SEARCH REPORT

Application Number

EP 99 30 3427

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.)
P, X	WO 99 16386 A (SCIMED LIFE SYSTEMS INC) 8 April 1999 (1999-04-08) * claims; figures *	1-24	A61F2/06 A61L31/00
X	WO 96 32907 A (SCHNEIDER USA INC) 24 October 1996 (1996-10-24) * page 3, line 27 - page 4, line 31 * * page 8, line 5 - page 11, line 21 * * claims; figures *	1-24	
X	WO 97 10011 A (SCHNEIDER USA INC) 20 March 1997 (1997-03-20) * claims; figures *	14-23	
X	WO 95 03083 A (BOSTON SCIENT CORP) 2 February 1995 (1995-02-02) * claims; figures *	1-24	
D, X	WO 91 12779 A (MEDTRONIC INC) 5 September 1991 (1991-09-05) * page 4, line 4 - line 7 * * page 8, line 13 - page 9, line 18 * * claims; figure 5 *	1-13	
X	WO 95 10989 A (SCIMED LIFE SYSTEMS INC) 27 April 1995 (1995-04-27) * page 2, line 25 - page 8, line 17 * * claims; figures *	1-13	A61F A61L
X	US 5 634 946 A (SLEPIAN MARVIN J) 3 June 1997 (1997-06-03) * column 7, line 25 - column 9, line 52 * * claims; figures; examples *	1-24	
X	US 5 624 411 A (TUCH RONALD J) 29 April 1997 (1997-04-29) * claims; figures; examples *	1-17, 24	
		-/-	
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
BERLIN	18 July 2001	Kuehne, H-C	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background D : non-written disclosure P : intermediate document			
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Office

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Application Number
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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)	
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)	
X	US 5 634 899 A (SHAPLAND JAMES E ET AL) 3 June 1997 (1997-06-03) * column 7, line 1 - line 20 * * claims; figures 1,2,4 *	1-6,10, 11		
X	EP 0 815 806 A (CORDIS CORP) 7 January 1998 (1998-01-07) * column 8, line 8 - line 54 * * claims; figures *	1-13		
X	US 5 591 199 A (PORTER CHRISTOPHER H ET AL) 7 January 1997 (1997-01-07) * claims *	1		
X	WO 91 17744 A (JERNBERG GARY R) 28 November 1991 (1991-11-28) * claims *	1		
X	CH 649 916 A (SULZER AG) 28 June 1985 (1985-06-28) * claims; figures *	1		
D,A	US 5 591 227 A (SCHWARTZ ROBERT S ET AL) 7 January 1997 (1997-01-07) * claims; figures *	1		
D,A	US 5 599 352 A (SCHWARTZ ROBERT S ET AL) 4 February 1997 (1997-02-04) * claims; figures *	14		
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int.Cl.6)	
Place of search	Date of completion of the search	Examiner		
BERLIN	18 July 2001	Kuehne, H-C		
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document		
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ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.

EP 99 30 3427

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

18-07-2001

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9916386	A	08-04-1999	US	5972027 A	26-10-1999
			US	6253443 B	03-07-2001
WO 9632907	A	24-10-1996	AU	4952096 A	07-11-1996
			BR	9608021 A	02-03-1999
			CA	2216943 A	24-10-1996
			EP	0822788 A	11-02-1998
			JP	10506560 T	30-06-1998
			NO	974823 A	17-10-1997
			US	5837313 A	17-11-1998
			US	6120536 A	19-09-2000
WO 9710011	A	20-03-1997	US	5837313 A	17-11-1998
			AU	703805 B	01-04-1999
			AU	6965296 A	01-04-1997
			BR	9610607 A	04-05-1999
			EP	1019107 A	19-07-2000
			JP	11500047 T	06-01-1999
			NO	981066 A	08-05-1998
			US	6120536 A	19-09-2000
			ZA	9607625 A	16-04-1997
WO 9503083	A	02-02-1995	US	5674192 A	07-10-1997
			CA	2166101 A	02-02-1995
			EP	0708671 A	01-05-1996
			JP	9500561 T	21-01-1997
			US	5954706 A	21-09-1999
			US	5843089 A	01-12-1998
WO 9112779	A	05-09-1991	CA	2049973 A	29-08-1991
			DE	69110787 D	03-08-1995
			DE	69110787 T	04-04-1996
			EP	0470246 A	12-02-1992
			JP	5502179 T	22-04-1993
			US	5545208 A	13-08-1996
			US	6004346 A	21-12-1999
			US	5871535 A	16-02-1999
			US	5851217 A	22-12-1998
			US	5725567 A	10-03-1998
			US	5851231 A	22-12-1998
			US	5997468 A	07-12-1999
WO 9510989	A	27-04-1995	US	5735897 A	07-04-1998
US 5634946	A	03-06-1997	US	5213580 A	25-05-1993
			US	5575815 A	19-11-1996

For more details about this annex, see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.

EP 99 30 3427

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

18-07-2001

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5634946	A		US 5843156 A US 5749915 A US 5674287 A US 5749922 A US 5800538 A US 5947977 A AT 121954 T AU 4191989 A CA 1336755 A CA 1340257 A DE 68922497 D DE 68922497 T DK 418989 A EP 0431046 A EP 0649637 A HK 1004534 A JP 2836878 B JP 4501670 T WO 9001969 A	01-12-1998 12-05-1998 07-10-1997 12-05-1998 01-09-1998 07-09-1999 15-05-1995 23-03-1990 22-08-1995 15-12-1998 08-06-1995 14-09-1995 25-02-1990 12-06-1991 26-04-1995 27-11-1998 14-12-1998 26-03-1992 08-03-1990
US 5624411	A	29-04-1997	US 5464650 A EP 0623354 A JP 8033718 A US 5837008 A US 5679400 A US 5776184 A US 5824048 A	07-11-1995 09-11-1994 06-02-1996 17-11-1998 21-10-1997 07-07-1998 20-10-1998
US 5634899	A	03-06-1997	AU 1559595 A WO 9518649 A US 5865787 A	01-08-1995 13-07-1995 02-02-1999
EP 0815806	A	07-01-1998	US 5769884 A CA 2207751 A	23-06-1998 27-12-1997
US 5591199	A	07-01-1997	AU 6043496 A EP 0836448 A JP 11506957 T WO 9640000 A US 5766204 A	30-12-1996 22-04-1998 22-06-1999 19-12-1996 16-06-1998
WO 9117744	A	28-11-1991	AU 7909691 A CA 2082398 A DE 69131574 D DE 69131574 T EP 0528971 A	10-12-1991 15-11-1991 07-10-1999 04-05-2000 03-03-1993

EPO FORM P0459
For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.

EP 99 30 3427

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EPO file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

18-07-2001

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9117744 A		US 5290271 A		01-03-1994
CH 649916 A	28-06-1985	NONE		
US 5591227 A	07-01-1997	US 5599352 A US 5957971 A EP 0701802 A JP 8089585 A US 5697967 A US 6080190 A US 5571166 A US 5591224 A US 5510077 A US 5554182 A US 5800507 A US 5628785 A US 5849034 A DE 69326631 D DE 69326631 T EP 0566245 A JP 6007455 A	04-02-1997 28-09-1999 20-03-1996 09-04-1996 16-12-1997 27-06-2000 05-11-1996 07-01-1997 23-04-1996 10-09-1996 01-09-1998 13-05-1997 15-12-1998 11-11-1999 08-06-2000 20-10-1993 18-01-1994	
US 5599352 A	04-02-1997	US 5957971 A EP 0701802 A JP 8089585 A US 5591227 A US 5697967 A US 6080190 A US 5571166 A US 5591224 A US 5510077 A US 5554182 A US 5800507 A US 5628785 A US 5849034 A DE 69326631 D DE 69326631 T EP 0566245 A JP 6007455 A	28-09-1999 20-03-1996 09-04-1996 07-01-1997 16-12-1997 27-06-2000 05-11-1996 07-01-1997 23-04-1996 10-09-1996 01-09-1998 13-05-1997 15-12-1998 11-11-1999 08-06-2000 20-10-1993 18-01-1994	

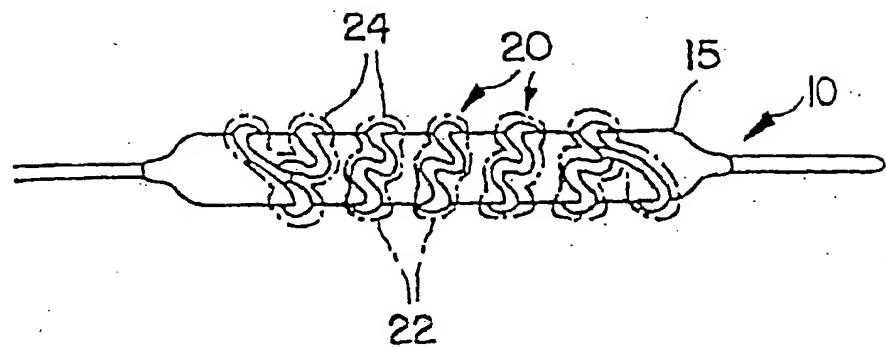


FIG. 1

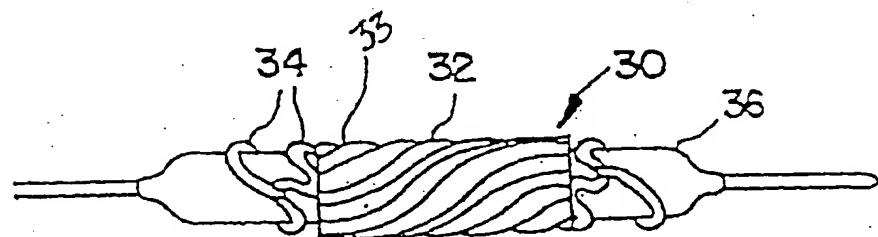


FIG. 2